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Published in:
Drug Discovery Today: Disease Models

DOI:
10.1016/j.ddmod.2018.10.002

Publication date:
2017

Drug Discovery Today: Disease Models
Vol. 25–26, 2017
Editors-in-Chief
Jan Tornell – AstraZeneca, Sweden
Andrew McCulloch – University of California, SanDiego, USA
Models of Neuroimmune and Neurodegenerative Diseases

Mouse models of central nervous system ageing

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Ageing is accompanied by decreased overall fitness and performance. Studying brain ageing in humans is challenging due to limited or no access to healthy tissue, limited opportunities for interventions and complicated confounding factors. The generation of mouse ageing models with uniform genetic backgrounds significantly contributed to understanding (brain) ageing at the molecular level. Research has focused on evolutionarily conserved mechanisms or pathways that control ageing to facilitate data extrapolation to humans. Understanding how these pathways contribute to pathological ageing may help us understand human central nervous system (CNS) ageing and assist in the development of possible therapeutic targets. In this review, we focus on the functional consequences and pathological changes in the CNS of ageing mouse models.

Section editor:
Professor Sandra Amor – Department of Pathology, Amsterdam UMC, VUMC site, 1081 HV Amsterdam, The Netherlands.

Introduction

Ageing is the main risk factor for many neurodegenerative diseases. Understanding how normal brain ageing transitions to pathological ageing is of vital importance to develop possible treatment for ageing associated central nervous system (CNS) pathologies.

To investigate CNS ageing, a range of ageing mouse models was developed, in view of the genetic similarity between mice and humans, their relatively short life span and amenability for genetic manipulation [1]. Human and mouse brain ageing exhibit many common features. On the pathological level, brain atrophy, neuronal loss, neuronal lipofuscinosis and reactive glial cells are observed following ageing in both human and mouse brain [2]. On a functional level, both humans and mice show an age-dependent decline in learning and memory and motor performance [3]. On a transcriptional level, common sets of genes are affected by ageing in mouse and human [4]. On an epigenetic level, DNA methylation is strongly correlated with ageing [5], and age-associated DNA methylation changes are relatively well conserved between humans and mice [6].

However, it is worth noting that there is very limited correlation between age regulated gene expression changes in mouse and human, indicating that the ageing process in the CNS of human and mice might be quite different [7,8]. Given that age regulation is quite different in different tissues and species [7], research has focused on evolutionarily conserved mechanisms that control ageing to facilitate data extrapolation to humans. These conserved pathways or mechanisms include genomic instability, epigenetic alterations, telomere attrition, mitochondrial dysfunction, loss of proteostasis and nutrient sensing pathways etc. [9,10].

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 https://doi.org/10.1016/j.ddmod.2018.10.002

In this review, mouse models that have been used to study CNS ageing and ageing-related diseases will be discussed with the main focus on pathological changes during CNS ageing.

Mouse models with genomic instability

Brain ageing is characterized by loss of genomic integrity [11]. Excessive DNA damage and insufficient DNA repair both can contribute to genomic instability during the ageing process [12]. Numerous mouse models with genomic instability have been established and extensively reviewed [13,14]. Here, we only focus on models with CNS ageing phenotypes. Detailed CNS phenotypes of these mice are described in Table 1.

Mouse models with excessive DNA damage

Atm-deficient mice

Ataxia-telangiectasia (AT) is a human genetic disorder caused by mutational inactivation of the ATM gene [15]. ATM plays a major role in maintaining genomic stability and DNA strand breaks accumulate in the brain of $Atm^{-/-}$ mice [16]. ATM dysfunction resulted in increased reactive oxygen species (ROS) production, which may induce the degeneration of cerebellar neurons [17]. The histological, immunohistochemical and electrophysiological properties of Purkinje cells (PCs) were not altered in cerebellum, however, these cells showed age-dependent defects in calcium spike bursts and calcium currents [18]. *Atm* deficiency induced progressive loss of dopaminergic neurons in the *substantia nigra* (SN) and GABAergic neurons in the *striatum* (STR) [19]. *Atm* deficiency was also shown to impair astrocyte-endothelial cell interactions, which could be the underlying mechanism for neurodegeneration [20].

BubR1 deficient mice

BubR1 is a mitotic checkpoint protein that is essential for the accurate separation of duplicated chromosomes during cell division. Reduced BubR1 expression induces aneuploidy, which affects genomic stability [21]. BubR1 insufficient mice ($BubR1^{H/H}$ mice) exhibited various motor deficits, including impaired motor strength, coordination, gait patterns and reduced locomotor activity. BubR1 expression is significantly reduced with natural ageing in the mouse brain, and $BubR1^{H/H}$ mice exhibit age related decline in hippocampal neurogenesis [22]. The oligodendrocyte progenitor cell proliferation and oligodendrocyte density were markedly reduced in brain and spinal cord, which further caused axonal hypomyelination [23]. Besides, $BubR1^{H/H}$ mice also showed cerebral degeneration and accelerated gliosis in the brain [24].

DNA methyltransferase deficient mice

DNA methyltransferase 1 (Dnmt1) is the most prevalent DNA methyltransferase that maintains genomic methylation stability. *Dnmt1* haploinsufficiency impaired learning and memory function in an age-dependent manner in mice [25]. In addition, conditional deletion of *Dnmt1* and *Dnmt3a* in neurons induced abnormal long-term plasticity in CA1 and deficits of learning and memory; however, no neuronal loss was observed [26].

DNA damage repair deficient mice

DNA damage alters the structure of DNA and most DNA damages undergo repair. Excess DNA damage is associated with ageing and cancer. There are several DNA repair pathways for different types of DNA damage. Deficiencies in DNA repair pathways cause progeria syndromes in humans and also affect the CNS [27]. Several ageing mouse models were established based on deletion or mutation of genes involved in DNA repair pathways.

Ercc1 deficient mice

Excision repair cross-complementation group 1 (ERCC1) is an essential component of multiple DNA repair pathways: nucleotide excision repair (NER), double-strand break repair and interstrand cross-link repair pathways [28]. Mice carrying a knock out and a hypomorpic allele for *Ercc1* showed age-dependent motor abnormalities and cognitive decline. Further studies revealed widespread astrogliosis, microgliosis and neuronal degeneration in the brain, and motor neuron loss in the spinal cord [28,29]. The mutant mice did not show altered synapse numbers and dendritic morphology in the hippocampus. However, $Ercc1^{\Delta/-}$ mice did show age-dependent changes in the proteomic composition and synaptic plasticity in the hippocampus [30]. A similar age-related cognitive decline and neurodegeneration were also observed in conditional knockout mice ($Ercc1^{f/-}$ *CaMKII-Cre*$^{+}$ mice), in which *Ercc1* deficiency was directed to excitatory forebrain neurons [28]. For microglia, we have shown that microglia in $Ercc1^{\Delta/-}$ mice exhibit a hypertrophic morphology with thickened primary processes and larger cell bodies at the age of 16 weeks. Functionally, $Ercc1^{\Delta/-}$ microglia displayed increased phagocytosis, proliferation and ROS production. $Ercc1^{\Delta/-}$ microglia displayed an exaggerated proinflammatory response to a systemic inflammatory lipopolysaccharide (LPS) challenge, indicative of a ''primed'' state. Transcriptome analysis also confirmed $Ercc1^{\Delta/-}$ microglia were primed, with a clear phagocytic and chemotactic profile and enhanced immune state [31,32].

Xpg$^{-/-}$ *mice*

The premature ageing syndrome Cockayne syndrome (CS) is characterized by growth failure, abnormal sensitivity to light and impaired development of the CNS [33]. In humans with CS, the DNA repair gene *XPG* that is involved in NER, homologous recombination repair and base excision repair (BER) is mutated. $Xpg^{-/-}$ mice exhibit multiple progressive features of CNS ageing, such as loss of hearing and vision, cognitive decline, motor deficits and early development of tremors [34]. $Xpg^{-/-}$ mice develop wide spread astrogliosis

Table 1. Selected CNS ageing phenotypes of ageing mouse models.

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Atm	Knockout (KO)	Impaired motor coordination; irregular gait patterns; reduced locomotor activity [81]	Smaller brain [82]	Progressive loss of DA neurons in the SN and GABAergic neurons in the STR [19]; no neuronal loss in the cerebellum; age-dependent defects in calcium spike bursts and calcium currents in PCs [18]	Progressive structural alterations in astrocytes of the retina [20,83]; astrocytes activation in cerebellum [84]			Ataxia-telangiectasia (AT)
BubR1	Homozygous hypomorpic mutaion	Impaired motor strength, coordination and balance; irregular gait patterns; reduced locomotor activity [23]	Smaller brain [23]	Reduced in dendritic spine density in the motor cortex and cerebellum [23]; deficits in neural progenitor proliferation and maturation in hippocampus [22]	Age dependent increase of GFAP-positive astrocytes in cortex and thalamus [24]	Age dependent increase of CD11b-positive microglia in cortex, hippocampus and thalamus [24]	Reduced oligodendrocyte progenitor cell proliferation and oligodendrocyte density in brain and spinal cord [23]	Lynch syndrome; mosaic variegated aneuploidy syndrome
Dnmt1 and *Dnmt3a*	Conditional *Dnmt1* and *Dnmt3a* KO in neuron	Age-dependent decline in learning and memory [26]	Smaller hippocampi [26]	Impaired neural plasticity in CA1 [26]				Cerebellar ataxia, deafness, and narcolepsy; hereditary sensory neuropathy
Ercc1	Hypomorphic mutation	Clasping of the hind-limbs, fine tremors and kyphosis, reduced motor performance and cognitive decline [29]	Smaller brain [29]	Age-dependent changes in the proteomic composition and synaptic plasticity in hippocampus [28,85]; progressive motor neuron loss in spinal cord [29]	Age-related increase in GFAP positive astrocytes in spinal cord and brain [29]	Age-related increase in Mac2-positive microglia in spinal cord and brain [29]; hypertrophic morphology with thickened primary processes and larger cell bodies; increased phagocytosis, proliferation and ROS production; priming state [31,32]		Cerebro-oculo-facio-skeletal (COFS) syndrome; xeroderma pigmentosum (XP)
Xpg	KO	Loss of hearing and vision, cognitive decline, motor deficits and early development of tremors [34]	Smaller brain [86]	Loss of PCs; abnormal dendritic morphologies and swollen proximal axon of PCs [35]	Age-related increase in GFAP positive astrocytes in spinal cord and brain [35]	Age-related increase in Iba-1 positive microglia in spinal cord and brain [35]		XP; COFS syndrome

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Csa	KO			Increase of p53-positive neurons in neocortex, cerebellar cortex and spinal cord; non-detectable levels of neuronal degeneration at 26 weeks of age [36]	Increase of p53-positive astrocytes in neocortex, cerebellar cortex and spinal cord; increase of GFAP-positive astrocytes in the medullary reticular formation [36]	Increase of Mac2-positive microglia in the white matter [36]	Mac2-positive microglia were frequently in close proximity of oligodendrocytes in spinal cord [36]	Cockayne syndrome (CS)
Csb	KO	Mild motor coordination deficits; reduced locomotion [87]						CS; COFS syndrome
Xpd	Knockin; G602D point mutation in *Xpd* locus	Less active within the first minute of an open field test; normal motor coordination and learning capacity [88]						XP combined with CS (XPCS); trichothiodystrophy (TTD)
Csb and *Xpa*	Neuron-specific KO *Xpa* in $Csb^{-/-}$ mice	Seizure behavior; reduced locomotor activity; reduced ambulatory behavior in open filed test [36]	Cortex atrophy [36]	Chronic neuronal degeneration in forebrain neurons [36]	Increase of GFAP-positive astrocytes in neocortex, hippocampus and amygdala [36]			CS; XP
Sirt6	Brain-specific *Sirt6* KO	Impaired non-associative (open field test) and associative (contextual fear conditioning) learning [39]						
Terc	KO	Impaired spatial learning and memory [42]	Decreased DG volume [42]	Loss of neurons in the CA1 and frontal cortex; reduced synaptic density in frontal cortex; impaired dendritic development and neuritogenesis in hippocampus [43]	Unchanged GFAP positive astrocytes density in cortex [43]	Age dependent decrease of CD11b positive microglial number and cell body volume in DG; increased microglial density in DG [42]; increased Iba-1 positive microglia density; reduced dendritic length and branch points of microglia in cortex and CA1 [43]		Dyskeratosis congenita (DKC)

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Tert	KO	Impaired spatial learning and memory [49]; aggressive and depressive behavior [48];		Impaired dendritic development and neuritogenesis in hippocampus [49]				DKC
Twnk	Overexpression of *Twinkle*$^{dup353-365}$ in DA neurons	Impaired motor coordination [89]		Loss of DA neurons in the SN [89]				Progressive external ophthalmoplegia; infantile-onset spinocerebellar ataxia; Perrault syndrome
Tfam	Conditional KO *Tfam* in forebrain neurons (MILON mice)	Decreased spontaneous motor activity; wobbly walking; aggressive behavior and/or hyperactivity in response to stress [90]		Massive neurodegeneration in the hippocampus, the somatosensory cortex and the piriform cortex [90]; extensive axonal degeneration in neocortex and hippocampus [91]	Increase of GFAP-positive cells in corpus callosum [91]			Mitochondrial DNA depletion syndrome
Afg3l2	Haploinsufficiency of *Afg3l2*	Impaired motor coordination; abnormal gait; clasping on tail suspension [92]		Progressive loss of PCs; morphological changes of PCs [92]	Astrocytes activation in granule layer of cerebellum [92]			Spastic ataxia; spinocerebellar ataxia
	Conditional KO *Afg3l2* in PCs	Unsteady gait [93]		Progressive loss of PCs; impaired mitochondrial protein synthesis in PCs [93]	Progressive activation of astrocytes in cerebellum; activated astrocytes are hypertrophic and express increased levels of GFAP [93]	Progressive activation of microglia in cerebellum; cellular hypertrophy and retraction of cytoplasmic processes of activated microglia [93]		
	Conditional KO *Afg3l2* in forebrain neurons			Degeneration of cortical neurons; increased pTau levels in cortical neuron [94]				
	Conditional KO *Afg3l2* in oligodendrocytes	Mild but significant impairment in motor coordination [95]					Axonal degeneration characterized by myelin thickening, vacuolization and disruption in spinal cord [95]	

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Afg3l1 and *Afg3l2*	Conditional KO *Afg3l2* and *Afg3l1* in oligodendrocytes	Impaired motor coordination [95]			Upregulation of GFAP protein level in the brain and spinal cord, astrocytes activation in corpus callosum [95]	Activated amoeboid-like microglia with thick processes in corpus callosum [95]	Progressive axonal demyelination in the spinal cord and brain; death of mature oligodendrocytes followed by compensatory repopulation [95]	Spastic ataxia; spinocerebellar ataxia
Spg7	KO	Abnormal gait characterized by uncoordinated movement of the hindlimbs; progressive impaired motor coordination [96]		Progressive degeneration of long spinal axons, optic nerves and sciatic nerves; mitochondrial abnormalities in synaptic terminals in spinal cord [96]				Spastic paraplegia
Spg7 and *Afg3l2*	*Spg7* KO and *Afg3l2* haploinsufficiency	Reduced cage activity; altered coordination of the hindlimbs during gait; loss of balance, uncoordinated gait, tremor and dystonic movements of the head [97]		Progressive degeneration and abnormal dendritogenesis of PCs; degeneration of hippocampal CA3 pyramidal neurons [97]	Astrocytes activation in hippocampus [97]			Spastic paraplegia; spastic ataxia; spinocerebellar ataxia
Phb2	Conditional KO *Phb2* in forebrain	Impaired learning and memory; impaired innate fear behavior and motor coordination; excessive pathological grooming behavior [98]	Smaller brain; forebrain atrophy [98]	Loss of neurons in DG and cornu ammonis (CA); increased pTau in hippocampus; shrinkage of the cell body and loss of processes of cortex neuron [98]	Progressive development of astrogliosis in DG [98]			
Aif	*Aif* hypomorphic harlequin mutation	Altered gait pattern and rhythm; lower locomotion speed [99]	Smaller cerebella [100]	Progressive loss of cerebellar granule cells and PCs [100]	Progressive astrogliosis in thalamus, cerebellum and the STR [101]	Microglia activation [101]		Cowchock syndrome; X-linked deafness-5

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
PstI	Specific expression of mito-*PstI* gene in DA neurons	Reduced exploratory behavior and spontaneous activity; impaired motor coordination [102]		Progressive loss of DA neurons in SN; reduced DA neuron projection and altered neurotransmitter production in the STR [102]				Hereditary pancreatitis
	Expression of mito-*PstI* in forebrain neurons	Abnormal limb-clasping; impaired motor coordination; impaired spatial learning and memory [103]	Smaller brain; cortical atrophy [103]	Massive neurodegeneration in the STR [103]	Increased GFAP protein level in STR, hippocampus and cortex [103]			
	Specific expression of mito-*PstI* gene in oligodendrocytes	Impaired motor coordination; reduced spontaneous activity; gait alterations; trunk instability; loss of tail tone; stiff and wobbly walking; reduced rearing behavior [104]			Astrogliosis in spinal cord [104]	Microgliosis in spinal cord [104]	oligodendrocyte loss, demyelination, and axonal damage in the spinal cord [104]	
Becn1	Heterozygous KO *Becn1* in APP transgenic mice			Reduced neuronal autophagy; synaptodendritic degeneration; neuron loss [105]		Increased CD68 expression and unchanged Iba-1 expression in frontal cortex [105]		
	Conditional KO *Becn1* in PCs	Abnormal gait and ataxic behavior [106]		Swollen dystrophic axons of the PCs; rapid degeneration of PCs [106]				
	Conditional KO *Becn1* in cortical and hippocampal neurons			Reduced neuron density in CA1 [106]				

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Atg7	Conditional KO *Atg7* in CNS	Abnormal limb-clasping reflexes; tremor; impaired motor coordination [107]	Cortex atrophy [107]	Loss of PCs; neuron loss in hippocampus [107]	Increased GFAP expression in the cerebral cortex [107]			
	Conditional KO *Atg7* in motor neurons of $SOD1^{G93A}$ mice	Hindlimb tremor [108]		Progressive loss of motor neurons [108]	Decreased GFAP expression in spinal cord compared to $SOD1^{G93A}$ mice [108]	Decreased Iba-1 expression in spinal cord compared to $SOD1^{G93A}$ mice [108]		
	Conditional KO *Atg7* in PCs	Impaired locomotion and motor coordination [109]		Axonal dystrophic swelling; degeneration of PCs [109]				
	Conditional KO *Atg7* in forebrain neurons	Impaired contextual fear memory and cued fear memory [110]		Progressive degeneration of hippocampal CA1 neurons; increased pTau-positive inclusions in neurons [110]				
	Conditional KO *Atg7* in DA neurons	Impaired locomotion [111]		Delayed DA neuron degeneration in midbrain; early degeneration of nigrostriatal axons; reduction in striatal DA levels; dystrophic dendrites; accumulation of alpha-synuclein in presynaptic terminals [111]				
FIP200	Conditional KO FIP200 in CNS	Impaired motor coordination; tremors and stiff movement; abnormal limb-clasping reflexes [112]	Smaller cerebella [112]	Progressive loss of neurons, spongiosis, and neurite degeneration in the cerebellum [112]				Hereditary breast-ovarian cancer syndrome
Smpd3	KO	Age-dependent decline of motor, coordination, and cognitive ability [54]		Increased neuron-specific marker *Mapt* and *Ttbk* expression; age-dependent neuronal dysproteostasis characterized by increased APP, amyloid-beta and pTau protein levels; age-dependent increase of neuronal apoptosis [54]	Unchanged astrocytes-specific markers *Eaac1* and *Glast1* gene expression level in brain [54]		Increased oligodendrocyte-specific *Plp* gene expression in brain [54]	

Table I (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Bip	Knock-in; *Bip* heterozygous mutation	Impaired motor coordination; paralysis and tremor; loss of righting reflex [56]		Increased ER stress, protein aggregation and neurodegeneration in the motoneurons of spinal cord [56]				
Igf-1	Conditional *Igf-1* KO in liver	Impaired spatial memory learning [58]			Increased number of GFAP positive cells in DG [58]			Insulin-like growth factor I deficiency
Igf1r	Astrocyte-specific KO of *Igf1r*	Impaired working memory [59]			Impaired mitochondrial function; deficient in glucose and amyloid-beta uptake in astrocytes [59]			IGF-1 resistance
Foxo1/3/4	KO			Axonal degeneration [60]	Extensive astrocytes activation in the brain and spinal cord [60]	Extensive microglial activation in the brain and spinal cord [60]		Alveolar rhabdomyosarcoma
Foxo1/3/4	Neuron-specific KO of *Foxo 1/3/4*	Auditory startle reflexes, the voluntary wheel-running activity, impaired locomotion and motor coordination; increased leg clasping behavior [60]			Astrocytes activation in the cerebellum [60]	Microglial activation in the cerebellum [60]		

Abbreviations: KO, knockout; DA, dopamine; SN, *substantia nigra*; GABA, gamma-aminobutyric acid; PCs, Purkinje cells; AT, Ataxia-telangiectasia; GFAP, glial fibrillary acidic protein; CA, *cornu ammonis*; ROS, reactive oxygen species; COFS, cerebro-oculo-facio-skeletal; XP, xeroderma pigmentosum; Iba-1, ionized calcium-binding adapter molecule 1; CS, Cockayne syndrome; XPCS, xeroderma pigmentosum combined with Cockayne syndrome; TTD, trichothiodystrophy; DG, *dentate gyrus*; DKC, dyskeratosis congenita; pTau, phosphorylated Tau; STR, *striatum*; APP, amyloid precursor protein; ER, endoplasmic reticulum.

and microgliosis in brain and spinal cord, starting at 4 weeks of age. At 14 weeks of age, astrogliosis was severe and associated with axonal swellings and loss of PCs in the cerebellum. The genotoxic stress marker p53 was detected in neurons, astrocytes and oligodendrocytes. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) showed a significant increase in apoptotic cells in the cerebrum at 4 as well as 14 weeks of age [35].

Csa$^{/}$ *and Csb* $^{/}$ *mice*

Csa and *Csb* are genes involved in transcription-coupled excision repair (TCR) In *Csa*$^{-/-}$ and *Csb*$^{-/-}$ mice, activated microglia and astrocytes are detected in the white matter. However, microglia activation was not observed in NER-deficient *Xpa*$^{-/-}$ and *Xpc*$^{-/-}$ mice. Therefore, next, TCR-deficient mice were generated with selective NER deficiency targeted to forebrain neurons. *Csb*$^{-/-}$/*Xpa*$^{c/-}$/*CamKIIα-Cre* mice displayed dramatic age-related neuronal loss, behavioral abnormalities, and brain atrophy in the forebrain [36].

Sirt6 deficient mice

Sirtuins (SIRT1–SIRT7) are an evolutionally conserved family of NAD^{+}-dependent deacetylases, and play a critical role in brain ageing and neurodegenerative diseases [37]. SIRT6 promotes DNA repair and its activity declines with age. Sirt6 overexpression expanded life span in male mice [38]. *Sirt6* knockout mice exhibit an accelerated ageing phenotype and die prematurely. *Sirt6* specific depletion in the brain results in increased DNA damage, Tau phosphorylation and learning defects [39].

3xTg/Polβ$^{+/}$ *mice*

DNA polymerase beta (Polβ) is a primary polymerase involved in BER. Disruption of Polβ induced growth retardation and post-natal lethality in mice. A 50% reduction in Polβ levels (heterozygous for *Polβ* gene) aggravated the phenotypes of 3xTg Alzheimer's Disease (AD) mice. Neuronal dysfunction, cell death and memory impairment were also shown to be more severe than in the 3xTg AD mice or *Polβ*$^{+/-}$ mice. Pathway comparison analysis of human and mouse microarray data revealed that the combined 3xTg/*Polβ*$^{+/-}$ transgenic mouse is more similar to human AD patients than the 3xTgAD or *Polβ*$^{+/-}$ mice [40].

Telomere attrition mouse model

Telomere shortening is observed in all eukaryotes [41]. Mice carrying a homozygous germ line deletion for the telomerase RNA component gene (*Terc*) showed complete loss of *Terc* expression and telomerase activity. For the *Terc*$^{-/-}$ mice, the telomeres become shorter during successive generations of mating due to the replication end-point problem, usually resulting in phenotypic changes after the third generation. Third generation T*erc*$^{-/-}$ mice showed impaired spatial learning memory, and accordingly, the dentate gyrus (DG) volume and brain weight were decreased in the *Terc*$^{-/-}$ mice [42]. Further study revealed reduced neurogenesis in the DG and loss of neurons in the hippocampus and frontal cortex in third generation *Terc*$^{-/-}$ mice [43]. Telomere dysfunction also led to reduced microglial numbers and cell body volume in DG, nevertheless, telomere shortening did not affect microglial proliferation or induce an ageing phenotype [42,43]. *Terc*$^{-/-}$ microglia also exhibited an enhanced pro-inflammatory response to peripheral LPS stimulation. However, unlike *Ercc1*$^{\Delta/-}$ microglia, this enhanced response is correlated with brain infiltration and blood–brain barrier dysregulation rather than age-related microglia priming [44]. *Terc* deficiency was also studied in combination with several age-related disease mouse models. Telomere shortening was shown to accelerate the amyotrophic lateral sclerosis (ALS) phenotypes in SOD1^{G93A} transgenic mice and Parkinson's disease (PD) phenotypes in (Thy-1)-h[A30P] α-synuclein transgenic mice [45,46]. Surprisingly, telomere shortening reduced AD amyloid pathology in APP23 transgenic mice [43].

Telomerase reverse transcriptase (TERT) is the catalytic subunit of the telomerase complex. Its deficiency also induced ageing phenotypes quite similar to T*erc* $^{-/-}$ mice [47]. What differed is that TERT deficiency induced aggressive and depressive behaviors in a mouse brain structure-specific manner [48]. *Tert* gene knockout mice also display impaired spatial memory, dendritic development and neuritogenesis [49]. Detailed CNS phenotypes of these mice are described in Table 1.

Mouse models with mitochondrial dysfunction

It is well accepted that mitochondria play a central role in ageing and neurodegenerative diseases [50]. Commonly used mouse models with mitochondrial dysfunction include dopaminergic neuron specific Twinkle transgenic mice, mitochondrial late-onset neurodegeneration (MILON) mice, mitochondrial quality control gene *Afg3l2, Spg7*, *Phb2* and *HtrA2/Omi*-deficient mice, apoptosis-inducing factor *Aif* deficient mice and mito-PstI transgenic mice all showed substantial brain ageing and neurodegeneration phenotypes [51]. Detailed CNS phenotypes of these mice are described in Table 1. Due to premature death of *HtrA2/Omi* deficient mice, this mouse model is not discussed here [52].

Mouse models with deficits in proteostasis

Loss of proteostasis is observed in many neurodegenerative diseases such as AD and PD. In mammals, proteostasis is maintained by chaperones and two proteolytic systems, the ubiquitin-proteasome and the lysosome-autophagy systems [10]. Autophagy-deficient mice showed ageing related changes and neurodegenerative changes that resemble those associated with ageing [53], among them, *Becn1*, *Atg7* and FAK family-interacting protein of 200 kDa (FIP200) deficient mice showed neurodegeneration phenotypes (see Table 1).

Defects in the sphingomyelinases gene *Smpd*3 resulted in age-dependent neuronal dysproteostasis in *Smpd*3$^{-/-}$ mice, causing accumulation of APP, Aβ, and phosphorylated Tau (pTau) in neurons. The deficient mice also showed age-dependent decline of motor activity, coordination and cognitive ability [54]. Endoplasmic reticulum (ER) is important to maintain proteostasis, as approximately 30% of proteins are synthesized and processed there. ER stress is also a common pathological signature in a variety of diseases, including neurodegenerative disease [55]. Binding immunoglobulin protein (BiP) is central for ER function and mutant BiP mice exhibited motor disabilities during ageing. Degeneration of motoneurons and accumulations of ubiquitinated proteins were also found in the spinal cord [56].

Mouse models with deficits in nutrient sensing

The insulin/insulin-like growth factor 1 (Insulin/IGF1) signaling pathway is evolutionarily conserved and involved in growth, development, metabolic homoeostasis and also CNS ageing [57]. IGF1 is a neuroprotective hormone that is mainly produced in the liver. Conditional, liver-specific inactivation of the *Igf1* gene induced an age-associated decline in learning memory. Further study identified astrocytosis and increased neurochemical disturbances in the DG area [58]. Reduced hippocampal IGF-1 receptor (IGF1R) expression is associated with age-related decline in learning, and astrocyte-specific knockout of IGF1R was demonstrated to induce impairments in working memory [59]. Forkhead box O (FOXO) transcription factors play a pivotal role in the IIS/PI3K/Akt signaling pathway. They are important determinants of ageing and longevity [60]. FOXO expression progressively increases in ageing human and mouse brains [61]. Conditional knockout of *Foxo* 1, 3, and 4 in neurons and glia cells induced an accelerated ageing phenotype in mice, manifested by axonal tract degeneration and gliosis [61].

Senescence accelerated mouse-prone (SAM-P) mice

The SAM-P mice are naturally occurring mouse lines that display a series of accelerated ageing phenotypes. At present, there are eight strains of SAM-P. It is noteworthy that each SAM-P strain has relatively strain-specific pathological phenotypes [62]. Since SAM-P/8 and SAM-P/10 display deficits in learning and memory, these strains were extensively used to investigate CNS ageing. A variety of age-associated alterations involving neurons, glia and blood brain barriers have been identified in SAM-P/8 and SAM-P/10 mice brain. SAM-P/8 could also serve as an animal model for AD and other dementias as age-related increases in pTau and amyloid accumulation were also observed in the hippocampus of SAMP8 mouse brains [63]. The 3xTg-AD transgenes in a SAM-P/8 background showed deficits in spatial memory and female-specific aggravation of AD pathology characterized by activation of astrocytes and increased accumulation of pTau and amyloid in the brain [64]. Some epigenetic alternations associated with ageing and neurodegeneration were also identified in the SAMP-P/8 brain [65,66].

Promising therapeutic targets

Although ageing itself is an inevitable process, interventions could be applied to extend both lifespan and health-span. A longevity study in monozygotic twins indicated that life span is determined largely by environmental factors rather than genetic factors [67]. Work on mouse models of ageing has not only contributed to the identification of many of the molecular pathways involved in ageing, but also have provided possible targets for the treatment of age-related CNS decline. Epigenetic signatures are proposed to function as biomarkers of ageing, for example, the DNA methylome can help to measure human ageing rates [5]. Epigenetic modifications are considered to be dynamic and reversible, making it an attractive therapeutic target. Chromatin modifying compounds such as sirtuin modulators and histone deacetylase inhibitors are thought to provide a promising treatment for neurodegenerative diseases [68,69].

In recent years, senescent cells are recognized as a new target for age-related disease. In mouse, clearance of p16Ink4a-positive senescent cells was shown to delay ageing-associated phenotypes in *BubR1*$^{H/H}$ mice [70]. Fuhrmann-Stroissnigg et al. established a drug-screening platform to identify senolytic compounds using *Ercc1*$^{-/-}$ primary murine embryonic fibroblasts. Through this platform, they successfully identified an HSP90 inhibitor, 17-DMAG, which could extend health-span and delay the onset of several age-related symptoms in *Ercc1*$^{\Delta/-}$ mice [71]. Microglia are shown to undergo age-dependent degeneration, increasingly displaying a primed or hyperreactive, pro-inflammatory phenotype and a deficiency in phagocytosis and chemotaxis. Senescent microglia are believed to be involved in switching normal brain ageing to pathological ageing [72]. The rejuvenation of senescent microglia was already shown to be a potential druggable target [73]. However, so far, there is no evidence whether microglia senolysis could restore normal function and revert or halt CNS ageing phenotypes.

Dietary restriction increases lifespan or health-span in all investigated eukaryote species [10]. A similar effect is seen when the activity of nutrient-sensing pathways is reduced by mutations or chemical inhibitors [74], indicating that nutrient-sensing pathways could provide promising targets to slow ageing. For example, the Insulin- and IGF-1-signaling pathway, the mammalian target of rapamycin (mTOR) pathway and the AMPK pathway are involved in nutrient sensing. And, manipulation of these pathways could increase lifespan and delay multiple aspects of ageing [10,75,76].

Conclusions

Studying brain ageing in humans is challenging due to very limited or no access to healthy tissue, limited opportunities

for interventions and human ageing in general is complicated by confounding factors like environment, nutrition, medical history, medication, education etc. The generation of mouse models with uniform genetic backgrounds significantly contributed to our understanding of ageing at the molecular level. However, conclusions must be drawn with caution because the results obtained from inbred mice may not represent the species as a whole [77]. Also, the mouse models cannot recapture all the brain ageing phenotypes in human, nor reliably predict age-related changes in humans owing to differences in the ageing process in human and mouse.

Though the mouse models described here have been used to identify molecular mechanisms of ageing, and to identify possible therapeutic targets, their use in the development of therapies and in particular the translation to the human situation is still not well developed [78]. In case of AD, for example, gene mutations that lead to AD-like phenotypes in young animals do not fully mimic human AD in older patients and therefore the predictive value of testing drugs in such models is limited [79].

Nonhuman primates are more similar to humans in how they experience ageing processes, which include ageing related pathologies like cancer, diabetes, arthritis, cardiovascular disease, and neurological decline. However, their substantial size, long lifespan, and the associated expense are prohibitive factors in their large scale-use for research into ageing. Nonetheless, they could provide a crucial component between the bench and the bedside [80]. In this review, we mainly focused on the functional consequences and pathological changes resulting from conserved pathways dysfunction in brain ageing. Understanding how these conserved pathways contribute to pathological ageing may help us to get a better understanding of brain ageing and develop possible treatment strategies. Finally, it is worth noting that the ageing process involves multiple organs and tissues, and the influence of peripheral organs on CNS ageing cannot be ignored.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by a China Scholarship Council (CSC) and Graduate School of Medical Science (GSMS) joint fellowship to Yang Heng. Susanne M Kooistra is funded by the Netherlands Organisation for Scientific Research (NWO, VENI, #016.161.072) and the MS Research Foundation.

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